Alberta Heritage Foundation
for Medical Research

LOW LEVEL LASER THERAPY FOR WOUND HEALING: AN UPDATE

Anita Simon

October 2004

IP22 Information Paper

© Copyright Alberta Heritage Foundation for Medical Research, 2004.

Reproduction, redistribution or modification of the information for any purposes is prohibited without the express written permission of the Alberta Heritage Foundation for Medical Research.

Comments relative to the information in this paper are welcome and should be sent to:

Director, Health Technology Assessment Unit
Alberta Heritage Foundation for Medical Research
1500 10104 - 103 Avenue
Edmonton, AB T5J 4A7 CANADA
Tel: (780) 423-5727 Fax: (780) 429-3509
Web address: www.ahfmr.ab.ca
E-mail: info@ahfmr.ab.ca

ISBN 1-894927-02-8 (Print)
ISBN 1-894927-03-6 (On-Line)

ISSN: 1706-7863

Alberta's health technology assessment program has been established under the Health Research Collaboration Agreement between the Alberta Heritage Foundation for Medical Research and Alberta Health and Wellness.

105-01197/

ACKNOWLEDGEMENTS

The Alberta Heritage Foundation for Medical Research is grateful to the following persons for provision of information and/or comments on the draft report.

- Dr. Cheryl Raiwet, Capital Health, Edmonton, Alberta
- Dr. Gordon Searles, Western Canada Dermatology Institute, Edmonton, Alberta

Information Services Support

Ms. Leigh-Ann Topfer, Canadian Coordinating Office for Health Technology Assessment, Edmonton, Alberta.

CONFLICT OF INTEREST

Conflict of interest is considered to be financial interest, either direct or indirect, that would be affected by the research contained in this report, or creation of a situation where an author's judgement could be unduly influenced by a secondary interest such as personal advancement.

Based on the statement above, no conflict of interest exists with the author of this report.

The views expressed in the final report are those of the Foundation.

EXECUTIVE SUMMARY

A technology assessment was conducted to assess the effectiveness of low level laser therapy (LLLT) in the treatment of chronic wounds, specifically leg ulcers and pressure sores. Seven databases were searched in addition to relevant library sections, web sites of practice guidelines, regulatory agencies, evidence-based resources and other Health Technology Assessment related agency resources to identify clinical trials and relevant clinical information from 1999 onwards. Nine clinical trials were identified and a critical analysis of these trials was performed to meet the objectives. The following findings and conclusions were made as result of this analysis and literature search:

- Low level laser therapy (LLLT) has been used in the treatment of wounds. Issues related to use of the technology in this application are definition of standard protocols and evidence of effectiveness.
- Low level lasers most commonly used for wound treatment are the gallium arsenide (GaAs), gallium aluminum arsenide infrared semiconductor (GaAlAs) and the helium neon (HeNe) devices.
- Differences exist in the delivery of LLLT. Variables include laser type and wavelength, the use of a single wavelength or a combination of wavelengths, irradiance or dosage, beam divergence, spot size, frequency and duration of treatment, applicator placement (contact or non-contact), and, for pulsed devices, pulse duration and duty cycle.
- To date, neither Health Canada nor the US Food and Drug Administration have approved low energy lasers for use in wound healing.
- Systematic reviews of the literature indicate that the efficacy of LLLT in this application is not established although it poses little or no safety risk to patients. There is no good scientific evidence to support its use and mounting evidence to indicate it does not benefit wound healing.
- Any local use of LLLT in this application should be limited to research, in patients resistant to conventional therapy.
- Other, possibly more promising alternative therapies, such as electrical stimulation and ultrasound, should be considered as adjunct therapies to conventional wound healing practices.

CONTENTS

Acknowledgements i

Executive Summary ii

Introduction 4

Description of LLLT technology 4

- Wavelength 5
- Energy 5
- Energy Density 6
- Power Density 6

Regulatory Considerations 6

- Health Canada 7
- U.S. Food and Drug Administration 7

Evidence of Efficacy and Effectiveness 7

- Best evidence 7

Discussion 15

Basic Principles of Wound Healing 16

- Conventional wound therapy 17
- Current wound management practices in Alberta 18

Recommendations for Alberta 19

Appendix A: Methodology 22

Appendix B: NPUAP Staging Criteria 26

Appendix C: AHCPR Supported Clinical Practice Guidelines for the Treatment of Pressure Ulcers 27

Appendix D: Canadian Association of Wound Care Recommendations for Practice 28

References 32

Tables and Figures

Table 1: Studies of LLLT on open wounds 9

Table 2: Cells Involved in Healing 16

Figure 1: Phases in wound healing 17

INTRODUCTION

Research into the role of low level laser therapy (LLLT), also known as low intensity and low power therapy, began in the late 1960s in Eastern Europe. The earliest experimental application of low power laser in medicine was reported in 1968 by Endre Mester in Hungary who revealed that a ruby laser treatment accelerated healing of mechanical wounds and burns in mice. Early laser reports were enthusiastic and anecdotal, but offered no understanding of mechanism. Since the 60s' the volume of research into LLLT has grown substantially and has focused on three areas to assess the value of LLLT in wound repair: cellular function, animal studies and human trials.

A request for updated information about the effectiveness of LLLT in chronic wound repair was given by the CBC program, Health Watch, in Halifax to the Alberta Heritage Foundation for Medical Research, Health Technology Assessment (HTA) Unit. This information is intended to summarize and update data presented in a Health Technology Assessment Report [1] completed in October 1999 on this same topic, requested by the Capital Health Authority. Since FDA approval has been granted for many LLLT devices since that time for pain management and additional research has been conducted regarding the efficacy of laser therapy for wound repair, another review of this technology is merited at this time to establish whether it could benefit medical practise in Alberta.

This technology assessment will focus on the efficacy, safety and effectiveness of LLLT in general terms, as supported by recent literature conducted between 1999 and 2004. Economic aspects of LLLT for wound repair are beyond the scope of this report. This report addresses the controversy that exists regarding the use of LLLT in clinical settings through a critical analysis of the quality of available research data.

The methodology used in this assessment is outlined in Appendix A. Only clinical studies were considered.

DESCRIPTION OF LLLT TECHNOLOGY

There are a number of different types of laser used for medical purposes, including crystalline laser medium, semiconductor lasers, liquid lasers and gas lasers. The carbon dioxide, argon, and neodymium:yttriumaluminum garnet (YAG) laser have found many applications in the surgical field. Such lasers often operate in the 10 to 100+ mW range with subsequent ability to vaporize and coagulate tissue.

LLLT or **"cold"** lasers use radiation intensities so low that it is thought that any biological effects that occur are due to the direct effects of radiation rather than the result of heating. Energies delivered are typically about 10 joules per cm^2, using lasers operating at powers of 50mW or less. LLLT devices have been advocated for relief of pain, healing of soft tissue disorders, and treatment of peripheral neuropathies and

primarily include the gallium-aluminum (GaAL), gallium-arsenide (GaAs), gallium-aluminum-arsenide (GaAlA) and helium-neon (He-Ne) laser. The He-Ne laser was the first laser available and is reported to have beneficial effects in both wound healing and dentistry. The He-Ne laser has the advantage that it emits red light, which is visible and therefore the blink reflex protects the eye from it. The GaAs and GaAlAs laser have been most commonly used for the treatment of pain and inflammation and in lower doses for wound healing as they have deeper tissue penetration than the He-Ne laser [2,3]. These lasers have the disadvantage that their light is invisible and therefore eye protection is required.

It is hypothesised that by exposing cells in a wound to the photon energy from LLLT, repair is enhanced by cellular proliferation or migration [4,5]. A number of mechanisms of LLLT have been postulated including ATP synthesis, collagen synthesis, fibroblast proliferation, phagocytosis of macrophages, activation of the immune system and acceleration of the inflammatory phase of wound healing [6].

Lasers are primarily defined by four main parameters: wavelength, energy, energy density, and power density. The following provides a brief description of these parameters.

Wavelength

The wavelength of a laser is determined by the medium from which it is generated. Wavelengths of low power lasers in common clinical use are 632.8nm (Helium Neon, gas) in the visible light range, 810nm (Gallium/Aluminium/ Arsenide, diode) and 904 nm (Gallium / Arsenide, diode) in the infrared region of the light spectrum. Other wavelengths are used more commonly in surgical settings. The wavelength is the prime determinant of tissue penetration.

Energy

Energy is a measure of the dose of laser given in any treatment. Energy, expressed as Joules, is related to the power of the laser and the duration of irradiation so that a higher power laser takes less time to generate the required number of joules than a lower power laser. It is calculated from the formula:

$$E = (P)(t)$$

Where:

E = Energy (Joules)

P = Power (Watts)

t = Time of irradiation (seconds)

The range of powers of laser devices used varies from 1.5 to 100 mW.

Energy Density

Doses for biostimulation of wounds are defined by the Energy Density. It is calculated from the formula:

$\rho_E = E/A$

where:

ρ_E = Energy Density (Joules/ cm^2)

E = Energy (Joules) – as defined above

A = Area of laser spot size (cm^2)

Based on empirical findings, the optimal dose for biostimulation is regarded as $4J/cm^2$. However, a recent study suggests higher energy densities (10.6 or 12 J/ cm^2) are required to produce clinical effect in wound repair [7].

Power Density

Power Density is a measure of the potential thermal effect of laser. It is fixed by the characteristics of the machine for any given power output and spot size. It is calculated from the formula:

$\rho_P = P/A$

where:

ρ_D = Power Density (Watts/ cm^2)

P = Power (Watts)

A = Area of probe tip (cm^2)

A sensation of heat is produced by a power density of 10,000 mW/cm^2.

Despite similarities of dose and a convergence in laser choice, significant differences persist between treatment approaches. These differences include pulse rate, applicator placement (contact or non-contact), and the use of a single wavelength or a combination of wavelengths. Also of potential importance are the irradiance (power/unit area), beam divergence, spot size, delivery (fibre optic, direct), polarity, and for pulsed devices, pulse duration and duty cycle. Reported individual treatment times range anywhere from 35 seconds to 20 minutes. Any protocol development of laser therapy should preferably include consideration of all these parameters as well as information about site preparation, technique and number of treatments [8, 9].

Regulatory Considerations

The Health Protection Branch in Canada and the Food and Drug Administration (FDA) in the U.S. were contacted about regulatory status for low level lasers used for wound healing.

Health Canada

In Canada, low lever lasers are regulated as Class 2 or Class 3(a) devices under standards such as those written by the Canadian Standards Association (CSA), the American National Standards Institute (ANSI) and Underwriters Laboratories (UL). Such standards address laser safety in health care facilities, medical electrical equipment, and safety of diagnostic and therapeutic laser equipment. In Canada, lasers have not been approved for use in wound healing. Health Canada Device Licensing staff request a Device Evaluation Division Opinion before licensing a device for a novel indication such as promoting wound healing. The Regulations state that clinical data are required in support of efficacy prior to licensing. They also define the requirements for carrying out clinical trials in Canada.

U.S. Food and Drug Administration

In the United States, medical lasers are classified as Class II (Special Controls) and must have Section 510(k) premarket approval or premarket clearance from the FDA prior to marketing for any claimed human indication, unless specifically exempted by the FDA. To date, the FDA has not approved LLLT devices for wound healing but has granted approval in the past 2 years (2002-2004) to many low level laser therapy devices for pain management associated with carpel tunnel syndrome, chronic neck and shoulder pain and arthritis in humans.

Although there appear to be no safety concerns regarding low level lasers, there is not adequate clinical information to receive regulatory approval from Health Canada or the FDA as a therapy to accelerate wound healing.

Evidence of Efficacy and Effectiveness

Best evidence

Two systematic reviews have been performed in the past 5 years, with similar time frames, to establish the effectiveness of LLLT in wound repair. The Cochrane Wound Group Trials Register performed a systematic review of randomized controlled clinical trials (RCTs) evaluating the benefit of LLLT in the treatment of venous leg ulcers [2, 10, 11]. Wound care journals, conference proceedings and electronic databases (including Medline and Cinahl) were searched up until December 1999 for RCTs comparing LLLT with sham laser, no laser, or non-coherent light of other wavelengths. A total of four RCTs of laser therapy pertaining to treatment of venous leg ulcers were identified. Two RCTs compared laser therapy with sham, one with ultraviolet light and one with non-coherent, unpolarised light. Each of the studies contained very small numbers of participants with group sizes varying between three and 23. Neither of the RCTs comparing laser with sham found a significant difference in healing rates. Furthermore, no difference between laser and sham was observed when these studies were pooled by meta-analysis to obtain 88 patients in total. The only suggestion of

therapeutic benefit was shown in one three-armed RCT where a combination of laser and infrared light led to an improvement in the healing rates of venous ulcers [2, 6, 10, 11]. The Cochrane Review concluded that there is no evidence of any benefit associated with LLLT on venous leg ulcer healing and that additional research is required to ascertain whether a combination of laser and infrared light may promote ulcer healing [2, 6, 10, 11].

The second systematic review was conducted in the Netherlands and published by Lucas et al. for the period 1975-1998 [12]. This review reported there are no scientific arguments for the routine application of LLLT on wound healing in patients with venous leg ulcers, pressure sores or chronic wounds. This systematic review pointed out that the study quality of the four included RCTs was poor and insufficient and that the small sample sizes used may lack the statistical power to detect clinically relevant treatment outcomes [12].

In the literature search undertaken for the present assessment, a further nine primary studies of LLLT effectiveness for wound healing were identified and are summarized in Table 1 [7, 12-19].

Table 1: Studies of LLLT on open wounds

Study	Patient characteristics	Therapy	Outcomes	Comments
Schindl et al. 1999 [18] Non-controlled clinical trial	**n=20** (20 ulcers, variable origin, refractory to conventional wound treatment: diabetes, radio damage, autoimmune vasculitis, arterial insufficiency) **Prior ulcer treatment: min.** 3 wks (median 34 wks)	Sterile saline wet-to-dry dressings covered with gauze and cotton mesh wrapping. Patients also received HeNe laser at λ632.8 nm and 30 mW power output, energy density of 30 J/cm^2 , 3x/week until ulcers healed. Radiant exposure along wound edges. Duration study treatment: 4-45 wks (median 12 wks) # study treatments: 13-75 Time duration of each laser session not given.	Complete closure of all ulcers treated with HeNe laser in all patients within a median treatment of 12.5 wks.	The findings of this study failed to show an enhanced rate of wound healing with HeNe laser stimulation as compared to alternative therapies. Poor level of scientific evidence, very small patient sample*. Controlled, comparative clinical studies on a larger number of patients are needed to warrant the clinical efficacy of low-energy lasers in enhancing wound healing in humans. Appropriate observations made regarding cause of ulcer and wound size influencing closure and healing rate.
Lucas et al. 2000 [12] RCT (multicentre)	**n=20** (16 Stage III pressure ulcers) **Control group:** Median age: 88 yrs. (72-95) Median ulcer duration: 4 wks. **Treatment group:** Median age:87.5 yrs (73-92) Ulcer duration: 3 wks	Treatment group received GaAs LLLT as an add-on modality to conventional treatment. GaAs laser at λ904 nm and 8 mW power output, energy density of 1 J/cm^2, 5x/week for maximum of 6wks (less if ulcers healed). Radiant exposure area of 30 cm^2. Pulse frequency 830 Hz.	Change in wound size reported and did not differ between treatment and control groups. Treatment group: 83% decrease in wound area vs Control group: 95% decrease in wound size p=0.47 Did not report healing rate or % ulcers healed.	One of few multicentre trials. Good overall design, fair level of evidence, small sample size. Authors state results may indicate LLLT is ineffective or be a function of inadequate sample size. Sample size of at least 74 patients is recommended to detect a clinically and statistically significant difference between study groups.

THBO=topical hyperbaric oxygen
GaAs=gallium arsenide
HeNe=helium neon
GaAlAs=gallium aluminum arsenide
λ = wavelength
LLLT= low level laser therapy

Table 1: Studies of LLLT on open wounds (cont'd)

Study	Patient characteristics	Therapy	Outcomes	Comments
Schubert et al. 2001 [19] RCT (single-blinded)	**n=74** (Stage II or III pressure ulcers) **Control group:** n=37 Age: 85 y **Treatment group:** n=37 Age: 85 y	All patients had ulcers cleansed with saline then dried. Infection treated with cadexomer iodine-containing gel. Treatment group: infrared + pulsed monochromatic light (PML) Infrared wavelength: λ956 nm Red wavelength: λ637 nm Infrared power density: 55W/m^2 Red power density: 21W/m^2 Pulse frequencies: 78Hz, 702Hz, 8.58 kHz during first 5 treatments 15.6Hz, 287Hz, 31.2Hz following treatments Treatment 1-5x/wk for 10wks or until ulcer healed (wk1:5 times; wk 2:4 times; wk 3:twice; wk4 and beyond: once a week) Exposure time=9min, 3cm above ulcer	Fifteen patients did not complete the study (unclear how many from control and laser). There was a significant difference in healing rate between the laser and control groups. Weekly healing rate 49% > in treatment vs control group ($p<0.05$). Ulcer size (wk4): Treatment: 79% decrease Control: 57% decrease ($p< 0.05$) Ulcer size not reported or statistically compared for weeks 5-10.	Authors did not perform intent-to-treat analysis or compare treatments after week 4. Baseline and outcome ulcer sizes were not reported making validity or comparability between groups impossible to determine. Authors do not explain rationale for combining infrared red and PML and results can not exclude placebo effect or the possibility that one intervention (red or infrared light) is efficacious. Poor study design and treatment intervention (pulse frequency and treatment frequency varied throughout course of study), many uncontrolled variables, incomplete reporting and analysis, good sample size.
Lagan et al. 2001 [15] RCT (single-blinded)	**n=9** (20 post-surgical wounds) Mean age: 49 y (16-60 yrs) **Control group**: n=4 (wounds n=5) **Laser group:** n=5 (wounds n=7) **Study period:** 11 wks/patient	Control group: Post-operative dressings including use of dry nonadhesive gauze dressing used with Anaflex, antiseptic cream. Restricted to only one treatment method.] Laser group: GaAlAs laser at λ830 nm, 9 J/cm^2, average power 30mW, irradiance 300mW/cm^2. Treatment frequency per week not specified. Irradiation performed at sites around wound margin of each wound (3 points per wound).	Wound size, healing time, appearance, patient self-report pain assessed weekly. No difference in any outcomes between study groups. Control group: All patients showed improvement. 74.6% decrease in wound size at wk5. ($p=0.55$); 8 wk healing time ($p=0.28$) Laser group: 60.9% decrease in wound size at wk 5; 11 wk healing time.	Good study design, fair level of scientific evidence, small sample size. Authors state there appears to be no benefit to using LLLT in the healing of post-surgical wounds. May be a role for LLLT in chronic wounds rather than these acute stage wounds.

Table 1: Studies of LLLT on open wounds (cont'd)

Study	Patient characteristics	Therapy	Outcomes	Comments
Kawalec et al. 2001 [14] Non-controlled clinical trial	**n=16** (19 ulcers of all types, including venous, ischemic, neurotrophic and traumatic wounds) **Average age:** 63 y (45-81 yrs) **Mean ulcer duration:** 8 mo (1 wk-10 yrs) All patients continued their medications and antibiotic treatment.	Treatment: GaAlA laser at λ980 nm. Power = 5W. Radiant exposure, exposure duration, energy density not specified. Treatment: every 2 wks for at least 8 wks. Number of treatments >=4. No of treatments: >= 4	Wound size, bacterial count, patient satisfaction. Wound size decreased 9.4% at wk 8. Bacterial count decreased 45.9% at wk 8. 7/19 (37%) ulcers healed.	Authors state that LLLT is a valuable adjuvant to conventional therapy for the treatment of ulcers. Poor level of scientific evidence. Small sample size and small improvement in ulcer size. Larger, comparative study required.
Lagan et al. 2002 [7] RCT (placebo-controlled)	**n=15** (16 chronic venous ulcers) Placebo control group n=7 received conventional therapy + sham irradiation Treatment group n=8 received conventional therapy + LLLT **Mean age:** 69.9 y **Mean ulcer duration:** 11.3 mo.	Treatment group: GaAlAs laser plus conventional therapy Average power: 532 mW Energy density: 12 J/cm^2 Pulse frequency: 5 kHz Wavelength: λ904 nm Exposure time: 125 s Trtmts were 1x/wk, for 4 wks. Applicator just off wound (distance 0.5 cm from surface).	Wound size, wound reduction, pain (VAS), appearance. Wound reduction (wk 4): Laser group: 27.5% Control group: 22.5% Wound reduction (wk 8): Laser group: 54.9% No difference between treatments in wound size, wound reduction, pain or ulcer appearance reported.	Authors state there appears to be a cumulative or delayed effect to treatment that warrants further investigation as well as to establish optimal treatment parameters. No difference in wound healing or reduction or pain between treatment groups despite higher energy density used. Good study design, fair level of scientific evidence, very small patient sample size that may be masking treatment effect. Comparability between groups not reported or assessed.

THBO=topical hyperbaric oxygen
λ = wavelength GaAs=gallium arsenide
HeNe=helium neon
GaAlAs=gallium aluminum arsenide
LLLT= low level laser therapy

Table 1: Studies of LLLT on open wounds (cont'd)

Study	Patient characteristics	Therapy	Outcomes	Comments
Landau & Schattner 2001 [16] Prospective, uncontrolled, open study	**n=100** Patients with chronic diabetic foot ulcers refractory to prior ulcer treatment (4.5 ± 1.2 mo) **Age:** 64 (± 10 yrs) **Ulcer duration:** 7 ±5 mo.	Treatment: THBO (150 min x 2 to 3x/wk at up to 1.04 atm) plus HeNe laser at λ632.8 nm in addition to conventional therapy. Power = 5W. Energy density: 4 J/cm^2 Exposure time: 20 min Average number of treatments: 25 Trtmts were 2-3X/wk Average treatment duration: 3.2 mo	81% (81/100) ulcers healed. Recurrent ulceration at 18 mo follow-up 4% (3/81). Healing rate and ulcer volume or size measures not reported.	Not clear which of the two treatments was the effective modality. Authors acknowledge using patients as their own control in study design not ideal and that results could also be result of prolonging conventional treatment. Poor study design, insufficient control of confounding variables, no comparator. Adequate sample size.
Franek et al. 2002 [13] RCT (3 arm, placebo controlled)	**n=65** patients; leg ulcers ***Group A (conventional + LLLT): n=21*** Mean age: 65 (44-80 y) Ulcer duration: 41 mo. Ulcer size (cm^2): 15.76 Ulcer volume (cm^3): 3.67 ***Group B (conventional + placebo sham): n=22*** Mean age: 66 (41-88 y) Ulcer duration: 30 mo. Ulcer size (cm^2): 13.25 Ulcer volume (cm^3): 3.26 ***Group C (conventional therapy): n=22*** Mean age: 66 (43-86 y) Ulcer duration: 51 mo. Ulcer size (cm^2): 16.20 Ulcer volume (cm^3): 4.14	Group A: GaAlAs laser 1x/day, 5 times per week plus compressive and conventional pharmaceutical therapy Average power: 65 mW\ Energy density: 4 J/cm^2 Pulse frequency: 20 kHz Wavelength: λ810 nm Placebo group B: placebo treatment received sham therapy from identical-appearing light sources, from the same delivery system. Treatment duration: Group A: 4.5 wks Group B: 5 wks Group C: 5 wks.	Ulcer area, ulcer volume and degree of granulation. ***Ulcer area (post-treatment):*** Gp A: 11.51 (p<0.005) Gp B: 8.04 (p<0.003) Gp C: 13.22 (p<0.001) All ulcer areas significantly improved after treatment. No significant differences between groups. ***Ulcer volume (post-treatment):*** Gp A: 2.05 cm^3 (p<0.036) Gp B: 1.65 cm^3 (p<0.019) Gp C: 1.58 cm^3 (p<0.001) All groups significantly decreased ulcer volume with the most improvement observed in conventional therapy arm. Control group C showed only significant change in granulation.	Authors conclude laser stimulation did not have a significant impact on healing of crural ulcers, as measured by rate of change of ulceration area and volume, degree of granulation. Good study design, reporting of patient characteristics, adequate sample size, homogeneous treatment groups, control of confounding variables including placebo effect and concomitant therapy. Unclear if adequate blinding of outcome measures and no intent-to-treat analysis performed.

Table 1: Studies of LLLT on open wounds (cont'd)

Study	Patient characteristics	Therapy	Outcomes	Comments
Lucas et al. 2003 [17] RCT	**n=86** (Stage III pressure ulcers) **Control group:** n=47 received conventional therapy Mean age: 84 y Ulcer duration (wks): 3.3 ± 5.1 Ulcer size (mm^2): 350 ± 378 **Laser group**: n=39 received conventional therapy + LLLT Mean age: 81 y Ulcer duration (wks): 2.9 ± 4 Ulcer size (mm^2): 317 ± 396	Control group: therapy according to National (American) Pressure Ulcer Advisory Panel. No medications allowed that could affect wound healing (e.g. Corticosteroids) or changes in concurrent meds. Treatment group: GaAs laser plus conventional therapy. Average power: 532 mW Energy density: 1 J/cm^2 Pulse frequency: 830 Hz Wavelength: λ904 nm Exposure time: 125 s Trtmts were 5x/wk, for 6 wks. Applicator <=1mm off wound.	Wound size, wound reduction, wounds healed. 5 patients lost to follow-up. Intent-to-treat analysis performed. **Wounds healed:** Laser group: 18/36 (50%) Control group: 15/43 (35%) **Wound reduction:** Laser group: 5% Control group: 34% There were no adverse effects. No differences in % wounds healed or wound reduction between study groups.	Authors paid specific attention to group size, baseline prognosis and comparability between groups, patient withdrawal and missing data as well as blinding unlike many previous studies. Very good study design and level of scientific evidence, adequate sample size.

These studies were all conducted after 1999 and the timeframes employed in the systematic reviews to determine whether recent research supports the use of laser therapy for wound repair. They include six randomized controlled trials (one of which is double-blinded) and three uncontrolled clinical trials. Five of six RCTs reported no benefit of laser therapy to conventional therapy for wound care in patients with pressure ulcers, venous leg ulcers and post-surgical wounds [7, 12, 13, 15, 17]. Of the RCTs, only two had adequate sample size and acceptable design and methodology to provide a good level of scientific evidence and neither showed a significant increase in healing for the laser therapy group [13, 14]. Of these trials, only one compared the use of low-level laser to sham laser therapy to control for a possible placebo effect [13].

The RCT conducted by Schubert reported a benefit for low level lasers used LLLT in combination with pulsed monochromatic light had substantial design and methodological flaws [19]. Pulse frequency and treatment frequency varied throughout the course of the study and many confounding factors were uncontrolled for. Treatments ranged from 1 to five times per week, treatment duration was not held constant between groups and was a function of ulcer healing. Only favourable week 4 results were reported and no statistical analysis was performed beyond study week 4 while treatment was ongoing. Prognostic ulcer characteristics were not reported on or compared between groups and an intent-to-treat analysis was not performed despite an unexplained 20% accrual rate. Authors do not provide a rationale for combining infrared and PML and results can not exclude the possibility that only one intervention is efficacious or that the difference between treatment reflects a placebo effect. Although the Schubert investigation had the potential to provide a good level of scientific evidence with an adequate sample size of 74 patients, the lack of a comparator coupled with uncontrolled variables and treatment parameters as well as incomplete reporting invalidates the results.

In the two non-controlled studies conducted by Schindl [18] and Kawalec [14], laser therapy was administered to small sample sizes of 20 and 19 patients, respectively. In both studies, ulcers of variable origin were refractory to prior ulcer treatment, and conventional dressing therapy was maintained throughout the course of the study. In the Schindl study, all ulcers healed following HeNe laser therapy given 3 times per week for a median of 12 weeks [18]. In the Kawalec study, 39% ulcers healed , average wound size decreased 9.4% and bacterial count decreased 45.9% following 8 weeks of GaAlA laser treatment given once every 2 weeks [14]. Because both these studies were not comparative and patients served as their own controls while continuing conventional wound care, the observed wound improvement could merely have been a result of prolonged conventional therapy rather than the laser treatment given.

In the prospective, uncontrolled study conducted in 2001 by Landau and Schattner [16] involving 100 patients with chronic diabetic ulcers refractory to 14 weeks prior ulcer treatment, HeNe laser therapy was combined with topical hyperbaric oxygen, given

three times per week for an average of 3.2 months. Eight-one percent of ulcers were healed and only 4% of these recurred at the 18 month follow up visit. As with the clinical series previously cited, results are invalidated due to poor study design despite adequate sample size. Because no active comparator or placebo control was used, it is impossible to ascertain which of the interventions are effective or determine whether wound improvement is attributed to a placebo effect or, simply, the maintenance of continued conventional therapy.

These recent studies indicate there is no benefit for the use of low level laser therapy on wound healing in patients with leg ulcers, pressure ulcers or other chronic wounds. They support findings reported in earlier systematic reviews and suggest other, more promising alternative therapies should be considered as adjunct therapies including ultrasound and electrical stimulation. Additional research is required to assess whether treatment schedule and parameters could improve wound healing outcomes.

DISCUSSION

Human effects ascribed to lasers have often been the result of non-peer reviewed literature, anecdotal reports, uncontrolled studies, published abstracts, controlled studies in which the study methodology has been poorly described, as well as controlled studies with contradictory results. Well-controlled studies demonstrating wound healing are few. These results do not support the use of low intensity lasers for wound repair.

The most significant flaw in the LLLT literature is the absence of standardized protocols. Virtually all the studies, utilize significantly different study parameters. Such parameter differences include:

1) type of laser used and thus wavelength;
2) laser power delivered in milliwatts;
3) energy delivered to the tissues in joules/cm2;
4) laser pulse frequency in hertz;
5) laser pulse duration in milliseconds;
6) duration of laser application in minutes; and
7) frequency and duration of treatment.

Based on these and other methodology flaws, one cannot conclude that LLLT is an effective therapeutic modality for the treatment of wounds. Well-controlled trials are needed to determine whether this approach is effective, and, if effective, the optimal patient populations and treatment schedules. Future research should include detailed reporting of concomitant therapy and patient characteristics such as ulcer size, origin, severity, and duration, as these can have important effects on healing.

BASIC PRINCIPLES OF WOUND HEALING

Use of LLLT needs to be considered in the context of other standard approaches to wound healing.

Wounds can be acute, as in the case of surgery, or chronic. In a healthy individual with no underlying factors, such as diabetes or venous disease, an acute wound should heal within 3 weeks with remodelling occurring within the next year or so. Chronic wounds are defined as those which have *"failed to proceed through an orderly and timely process to produce anatomic and functional integrity, or proceeded through the repair process without establishing a sustained anatomic and functional result"* [20]. The flowchart in Figure 1 outlines five discrete steps in the wound healing process and Table 2 provides a framework for the underlying physiological stages that occur during wound repair.

'Re-epithelialization' is typically the stage where most chronic wounds stop in the healing process and what clinical practise must assist by taking into account the underlying causes and factors interfering with wound healing that may be multifactorial [20].

This report has focused on chronic wounds including venous stasis ulcers or a pressure ulcer/sores because these wounds impose significant medical and socioeconomic burdens to health care. One study involving acute post-surgical wounds has been included because of its good level of scientific evidence.

Table 2: Cells Involved in Healing

Phase of Healing	Days post injury	Cells involved	Analogy to House Building
Hemostasis	Immediate	Platelets	Capping off conduits
Inflammation	Day 1-4	Neutrophils	Unskilled laborers cleaning up site
Proliferation/Granulation	Day 4-21	Macrophages	Supervisor cell
		Lymphocytes	Specific laborers at site:
		Angiocytes	Plumber
		Neurocytes	Electrician
Contracture		Fibroblasts	Framers
		Keratinocytes	Roofers and siders
Remodeling	Day 21-2 yrs	Fibrocytes	Remodellers

Source [20]

Figure 1: Phases in wound healing

Hemostasis
- Occurs within minutes of tissue injury
- blood vessels constrict then relax
- intrinsic clotting cascade initiated through production of thrombin
- hemostasis and stable clotting of damaged vessel occurs
- platelets migrate to wound

↓

Inflammatory phase
- lasts up to 4 days post injury
- vasodilation/erythema leaking neutrophils into surrounding tissue
- neutrophils clean up tissue debris
- triggers neutrophils and macrophage migration into wound
- macrophage secrete chemotactic and growth factors such as fibroblast growth factor (FGF), epidermal growth factor (EGF), transforming growth factor beta (TGF and interleukin-1 (IL-1) which direct next stage of wound healing

↓

Proliferative phase (proliferation, granulation and contraction)
- starts 4 days post injury and lasts up to 3 weeks in an acute wound
- replacement of dermal tissues and sometimes subdermal tissues in deeper wounds

Simultaneous events that occur in this phase:
- fibroplasia: fibroblasts secrete collagen framework
- angiogenesis: angiocytes regenerate outer capillary layers, endothelial cells produce lining
- epithelialization: keratinocytes differentiate to form protective outer layer

↓

Remodeling or Maturation phase [Most chronic wounds halt at this stage of the healing process]
- 21 days to 2 years post injury
- fibrocytes remodel dermal tissues to produce greater tensile strength
- basement membrane proteins reappear in a very ordered sequence from the margin of the wound inward in a zipper-like fashion closing the epidermal defect. Chronic wounds typically do not make it to this stage, i.e. granulation may occur but epithelial cells do not migrate over and close the wound.

Conventional wound therapy

The efficient management of wounds requires a multidisciplinary team made up of physicians, clinical nurse practitioners, dieticians, social workers, occupational and physical therapists [20]. Conventional wound therapy involves two basic principles for all chronic wounds including pressure ulcers, venous leg ulcers and diabetic foot ulcers; 1) identify and control the underlying causes, and 2) provide an environment for moist interactive wound healing (dressings) [2, 21-23]. Compression therapy is considered standard intervention for the care of leg and foot ulcers while pressure ulcers require pressure reduction or pressure relief for ulcer healing to occur.

The classification and staging wounds is inevitably the first step for treating wounds, along with identifying underlying causes and factors that may affect healing. Staging of wounds follows the National Pressure Ulcer Advisory Panel (NPUAP) staging criteria in North America (see Appendix B).

In the literature, the AHCPR guidelines are most frequently cited for the care of pressure sores. In these guidelines, initial care of the pressure ulcer involves debridement, wound cleansing, the application of dressings, and possibly adjunctive therapy. In some cases, operative repair is required. Appendix B depicts the procedural flow, decision points, and preferred management path for ulcer care advocated by the AHCPR. The four basic components of the ulcer care plan are:

(1) debridement of necrotic tissue as needed on initial and subsequent assessments;

(2) cleansing the wound initially and with each dressing change;

(3) prevention, diagnosis, and treatment of infection, and

(4) using a dressing that keeps the ulcer bed continuously moist and the surrounding intact tissue dry.

Electrical stimulation is the only alternative therapy supported by these guidelines and may be considered for patients with Stage III or IV pressure ulcers that are refractory to more conventional treatments. To date, electrical stimulation has only been used by a small number of research centers.

Current wound management practices in Alberta

In Alberta, the Calgary Regional Health Authority (CRHA) follows the Canadian Association of Wound Care (CAWC) recommendations for practice for the treatment of venous ulcers and pressure sores which have developed clinical pathways and best practices for wound healing. The pathway was designed by a multidisciplinary team and is meant as a guide for health care professionals who treat patients with acute or chronic wounds. The Capital Health Authority (CHA) developed a Regional Wound Care Guideline for use by health care professionals in 1998 that was later revised and updated in 2001 [24] Like the CRHA, the CHA used a multidisciplinary team to produce their Guideline.

Both health authorities treat wounds using conventional therapy. However, they do mention alternative therapies in their literature. The S.W.A.T. (skin & wound assessment and treatment) Team of the CRHA uses the text *Chronic Wound Care* [25] as a guide for instruction on the use of alternative therapies in addition to following the best clinical practices of the Canadian Association of Wound Care for the treatment of venous, diabetic foot and pressure ulcers [26-28]. These publications state that clinical safety and efficacy of LLLT has not been established. Further controlled clinical studies on large numbers of patients are needed to confirm the clinical efficacy of low intensity

lasers on wound healing. Low intensity laser therapy should only be used as an adjunct treatment to conventional wound care.

The CHA mentions adjunctive therapies such as HBO, laser, ultrasound, and electrical stimulation. The CHA quotes the AHCPR's clinical practice guideline stating that it is the responsibility of users to ensure they are using a modality with demonstrated efficacy through clinical research, and that the user has the appropriate training to apply that modality.

RECOMMENDATIONS FOR ALBERTA

Recent published studies indicate LLLT is not effective in accelerating the wound healing process as an adjunctive treatment to conventional therapy. At this time, regional clinical practice should not be modified to incorporate LLLT in wound management. LLT use in Alberta should be limited to a research basis in patients with chronic ulcers resistant to conventional therapy only.

If local studies are to be conducted in Alberta, the following criteria should be met:

- **Study design.** Evidence of efficacy should be obtained through one or more RCTs that are double-blind, placebo-controlled and preferably multi-centre in design.
- **Protocol design and standardization.** Treatment parameters such as type of laser (and therefore wavelength), energy density, power density/irradiance, applicator placement should be constant between studies and centres for multi-centre studies. Treatment frequency and duration should also be standardized with duration a minimum of 6 weeks and up to 2 years, in accordance with observed healing times for chronic wounds. All treatment parameters should be well defined so that each centre participating in the study has an established protocol.
- **Patient selection.** Current scientific literature describes use of LLLT in heterogeneous populations of patients that do not allow comparisons between groups. Well defined comparators applied consistently in non-laser arms during any RCTs should be undertaken. Patient inclusion/exclusion criteria should control ulcer type, preferably ulcer cause as much as possible and ulcer severity/stage as these factors have been shown to significantly effect wound healing. Sample size should be at least 74 patients to have enough statistical power to detect differences between study treatments as reported by Lucas et al. [12]. Patients should be excluded with peripheral arterial disease, haematologic abnormalities, vasculitis, history of epilepsy, those receiving topical steroids around wound site, those receiving anticoagulant therapy, those receiving drugs known to cause photo-sensitivity reactions and these pose safety risks to the patients or will confound outcome measurement.
- **Clinical outcomes:** Outcomes should be well-defined and clinically meaningful such as percentage healed ulcers and total decrease in ulcer volume. Follow-up should be

long enough to obtain these outcomes (see protocol design section above). Weekly healing rates, bacterial counts, skin temperature and changes in epithelialization or granulation should not be considered adequate primary endpoints.

Studies of this sort are needed to better assess or support the use of LLLT technology in routine wound care. Similarly, more research is needed to evaluate other available technologies including ultrasound, electrical stimulation and electromagnetic therapy in wound healing as their roles as adjuncts to other proven therapies remain unclear.

In conclusion:

- The benefits of low level laser therapy for wound healing are not established. Although LLLT appears safe, there is no good scientific evidence to support its use and mounting evidence to indicate it does not benefit wound healing.
- Any local use of LLLT in this application should be for research purposes only and in patients resistant to all other conventional therapy.
- Other, possibly more promising alternative therapies should be considered as adjunct therapies to conventional wound healing practices before LLLT.
- In spite of 5 years having passed since the last AHFMR review, the findings are unchanged.